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Development and Characterization of Tinidazole Floating Drug Delivery System

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ABSTRACT

The oral route of drug administration is prioritized due to its advantages in patient compliance and convenience. Floating tablets have been chosen to facilitate a sustained and predictable drug delivery profile within the gastrointestinal tract, thereby managing gastric residence time through gastro-retentive dosage forms that offer novel and significant therapeutic alternatives. The primary objective in designing oral controlled drug delivery systems is to enhance predictability and bioavailability. Nevertheless, these systems encounter various physiological challenges, including the difficulty in maintaining localized control of drug delivery within specific regions of the gastrointestinal tract and the inherent variability of the gastric emptying process. In humans, gastric emptying typically occurs within 2-3 hours, primarily affecting the stomach and upper intestine, which can lead to incomplete drug release from oral controlled delivery systems, ultimately reducing the effectiveness of the administered dose. Ensuring close contact between the oral controlled drug delivery system and the absorbing membrane can optimize drug absorption and influence the absorption rate. These factors have prompted the development of oral controlled gastro-retentive dosage forms with enhanced gastric retention capabilities. Tinidazole floating tablets are utilized for the treatment and prevention of bacterial infections in the stomach and intestines.

Keywords: Bioadhesive Floating Matrix, Tinidazole, Polymers, Sodium Bicarbonate, Citric Acid, In Vitro Drug Release Studies.

INTRODUCTION

The oral administration of pharmaceuticals represents one of the most straightforward methods of drug delivery, attributed to its ease of use, high patient adherence, and versatility in formulation. Over the years, oral dosage forms have evolved significantly, ranging from immediate-release formulations to those designed for targeted delivery. Gastro-retentive dosage forms (GRDDS) notably enhance the duration of drug release, thereby extending dosing intervals and improving patient compliance. These systems facilitate controlled drug delivery for compounds with specific absorption windows by ensuring a sustained release of the drug prior to reaching its site of absorption, ultimately optimizing bioavailability. Tinidazole, an anti-parasitic agent, is effective against various protozoan infections, including those caused by Trichomonas vaginalis, amebiasis, and giardiasis. Furthermore, Tinidazole is recognized for its efficacy against anaerobic bacterial infections and is also beneficial in the management of Crohn's disease, antibiotic-associated Diarrhea, and rosacea.

MATERIALS

Tinidazole was sourced from Hetero Labs in Hyderabad, while the natural polymers and other chemicals utilized were of analytical grade.

METHODOLOGY

Drug and Excipient Compatibility Studies

Compatibility studies between the drug and excipients were conducted under accelerated conditions to assess their interaction. This involved creating a homogeneous mixture of the excipients and the drug, which was then placed in HDPE and LDPE bags. Glass vials were subjected to temperatures of 60°C and 40°C with 75% relative humidity for duration of four weeks, while LDPE bags were maintained at 40°C ± 75% relative humidity for the same period. Samples were periodically examined for any physical changes.

Formulation Development

Table-1: Composition of Tinidazole Floating Tablets

Ingredients	**Formulations**							
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**
Tinidazole	400	400	400	400	400	400	400	400
Sodium alginate	50	-	-	-	100	-	-	-
Tragacanth	-	50	-	-	-	100	-	-
Eudragit	-	-	50	-	-	-	100	-
HPMC	-	-	-	50	-	-	-	100
Lactose	135	135	135	135	85	85	85	85
Sodium bi carbonate (mg)	10	10	10	10	10	10	10	10
Magnesium stearate (mg)	3	3	3	3	3	3	3	3
Talc (mg)	2	2	2	2	2	2	2	2
Total wt. (mg)	600	600	600	600	600	600	600	600

Preparation of Formulation:

1. The drug and polymers are separately passed through a 40 # mesh, after which they are transferred to a poly bag and mixed for duration of three minutes.

2. Diluents and other excipients are then incorporated into the mixture. Finally, Glidant (Magnesium Stearate) and Lubricant (Talc) are added to the blend, which is mixed for an additional two minutes.

3. The lubricated blend is subsequently compressed using 10mm round punches.

Evaluation of Tablets

Weight Variation Test

This test serves as an in-process quality control measure to ensure that manufacturers maintain control over the weight variation of the compressed tablets. Various pharmacopoeias outline specific weight variation tests. These tests primarily involve comparing the weight of individual tablets (xi) from a sample with the established upper and lower percentage limits based on the observed sample average (x-mean). The United States Pharmacopeia (USP) has set forth limits for the average weight of uncoated compressed tablets, applicable when the tablet contains 50mg or more of the active ingredient or when the active ingredient constitutes 50% or more of the total weight of the dosage form.

Method:

Twenty tablets are weighed individually, and the average weight is determined. The weights of the individual tablets are then compared to the average weight. According to USP guidelines, no more than two tablets should deviate from the average weight by more than the specified percentages. Additionally, no tablet should differ by more than double the relevant percentage.

Table -2: Limits for Tablet Weight Variation Test

Average Weight of Tablet (mg)	**% Difference Allowed**
130 or less	10 %
From 130 to 324	7.5 %
> 324	5 %

Content Uniformity

The content uniformity test is conducted to verify that each tablet contains the specified amount of active pharmaceutical ingredient with minimal variation among tablets within a given batch. In light of heightened awareness regarding physiological availability, this test has been incorporated into the monographs for all coated and uncoated tablets, as well as all capsules intended for oral use, particularly for dosage forms that are 50 mg or smaller.

Method:

A random selection of 30 tablets is made, with 10 of these being assayed individually. The test is deemed successful if at least 9 out of the 10 tablets contain no less than 85% and no more than 115% of the labeled drug content, while the 10th tablet may contain no less than 75% and no more than 125% of the labeled content. Should these criteria not be satisfied, the remaining 20 tablets are assayed individually, ensuring that none fall outside the 85% to 115% range.

Friability

Tablets are often subjected to chipping, capping, or breaking due to friction and shock. The friability test is closely associated with tablet hardness and is designed to assess the tablet's ability to endure abrasion during packaging, handling, and transportation. This is typically measured using the Roche friabilator.

Method:

A specified number of tablets are weighed and placed in the apparatus, where they undergo rolling and repeated shocks as they drop 6 inches with each rotation. After four minutes of this process or 100 revolutions, the tablets are reweighed, and the weight is compared to the initial measurement. The loss attributed to abrasion serves as an indicator of tablet friability, expressed as a percentage. A maximum weight loss of no more than 1% of the initial weight of the tablets during the friability test is generally considered acceptable, and any broken or crushed tablets are excluded from consideration.

The percentage of friability is calculated using the following formula:

% friability = (W1 - W2) / W1 × 100

W1 = Weight of tablets before the test

W2 = Weight of tablets after the test

Floating Lag Time

The interval between the introduction of the tablet into the medium and its ascent to the upper one-third of the dissolution vessel is referred to as the floating lag time, while the duration for which the dosage form remains afloat is known as the floating or flotation time. These assessments are typically conducted in simulated gastric fluid or 0.1N HCl maintained at 37°C, utilizing USP dissolution apparatus containing 900 ml of 0.1N HCl as the dissolution medium.

In Vitro Drug Release Studies

The release of the drug from Tinidazole tablets was examined using a USP-II (paddle) apparatus with 900 ml of 0.1N HCl at a rotation speed of 50 rpm and a temperature of 37°C. At specified time intervals, 5-ml samples were collected, from which 1 ml was diluted to 10 ml for analysis via UV spectrophotometry at a wavelength of 296 nm.

Kinetics of Drug Release

To analyze the kinetics, the data obtained from in vitro release studies were plotted according to various kinetic models.

- Zero-Order Equation: %R = Kt

This model signifies an ideal release profile aimed at achieving prolonged pharmacological action. It is relevant for dosage forms such as transdermal systems, coated forms, osmotic systems, and matrix tablets containing poorly soluble drugs.

- First-Order Equation: Log% unreleased = Kt / 2.303

This model is suitable for investigating hydrolysis kinetics and the release profiles of pharmaceutical dosage forms that include water-soluble drugs in porous matrices.

- Higuchi Equation: $\%R=Kt^{0.5}$

This model applies to systems where the drug is dispersed within a uniform swellable polymer matrix, as seen in matrix tablets containing water-soluble drugs.

- Korsmeyer-Peppas Equation: $\%R=Kt^{n}$

This model is extensively utilized when the release phenomenon is involved.

Table-3: The Final Values Can Be Employed To Characterize Various Release Mechanisms

N	Mechanism
0.5	Fickian diffusion(Higuchi matrix)

0.5<n<1	Anomalous transport
1	Case- II transport(zero order release)
n>1	Super case- II transport

Stability Studies

The effectiveness of a formulation can only be assessed through stability studies. The primary aim of stability testing is to ensure the development of a stable product that guarantees safety and efficacy throughout its shelf life under specified storage conditions and peak profiles. The Tinidazole floating tablets were stored in plastic tubes containing desiccants at various ambient conditions, including room temperature, 40±2°C, and refrigeration at 2-8°C, for duration of 90 days.

RESULTS AND DISCUSSION

Drug-Excipient Compatibility Studies (FT-IR):

The compatibility of the drug with various excipients was assessed using the FTIR peak matching technique. The analysis revealed no new peaks or the disappearance of existing peaks in the drug-lipid mixture, indicating that there were no chemical interactions between the drug, lipid, and other components.

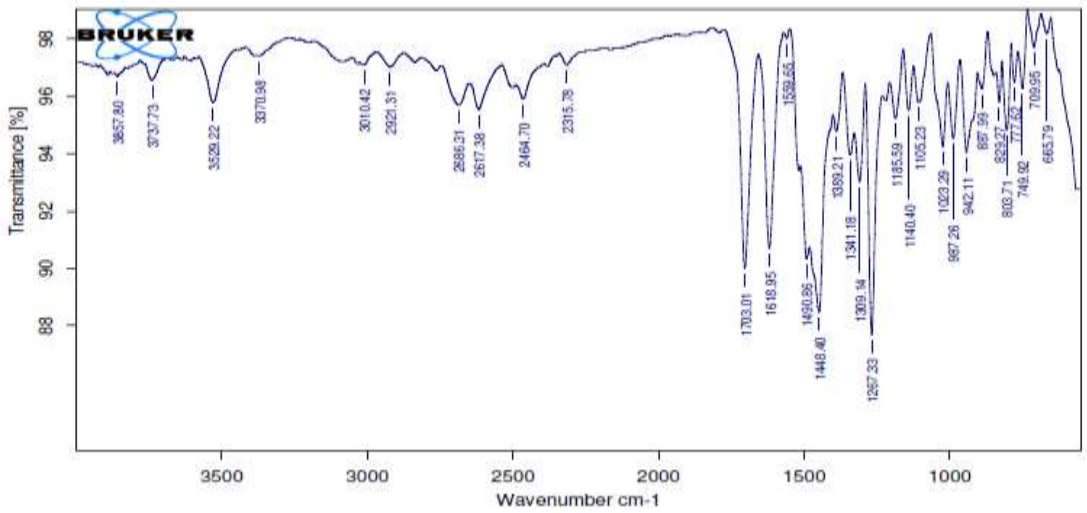

Fig-1: FT-IR Sample for Tinidazole

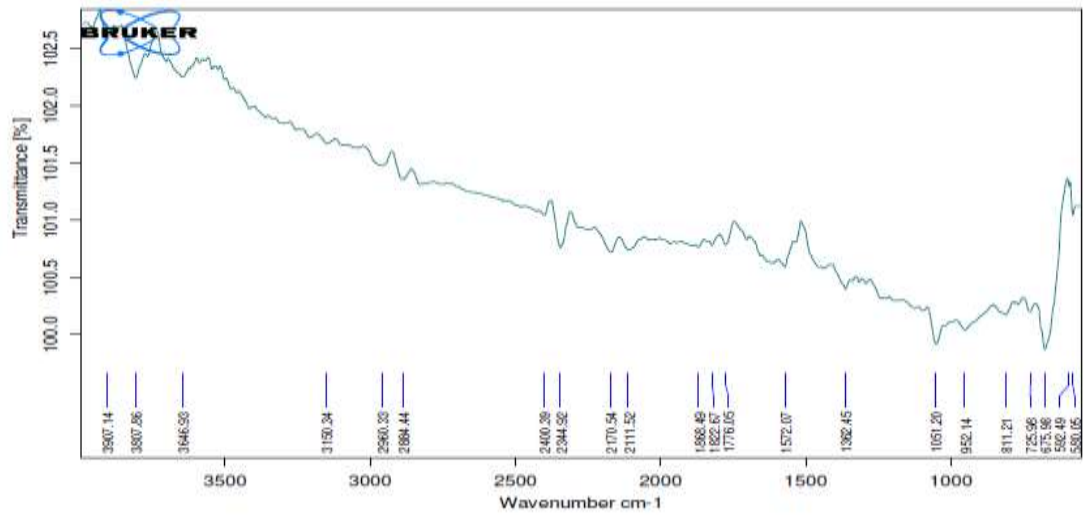

Fig-2: FT-IR Sample for Optimized Formulation

Evaluation of the Prepared Tablets

Table-4: Evaluation Parameters of Tinidazole Floating Tablets

Parameter	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**
Weight Variation	600	599	600	599	598	600	599	600
Thickness (Mm)	4.2	4.5	4.4	4.5	4.3	4.6	3.8	4.1
Hardness (Kg/Cm^2)	4.2	4.1	3.9	4.0	4.3	4.4	4.6	4.1
Friability	0.42	0.46	0.49	0.5	0.48	0.47	0.52	0.53
Content Uniformity	92.35	94.59	93.59	92.36	90.86	94.59	97.59	98.32
Floating Lag Time (Sec)	45	52	55	42	44	50	49	48

Floating Lag Time

The floating tablets of Tinidazole were developed utilizing the direct compression method. A total of eight distinct formulations were created, each employing varying ratios of polymers. These formulations were subsequently assessed for their floating lag time and buoyancy duration. The introduction of sodium bicarbonate facilitated the generation of carbon dioxide in the presence of the dissolution medium (0.1 N HCl). It was noted that the produced gas was encapsulated within the polymer matrix, resulting in a reduction of the tablet's density, thereby enhancing its buoyancy. The floating lag time recorded for the optimized formulation F8 was 48 seconds.

In Vitro Drug Release Studies

Samples were collected at specified time intervals and analyzed using spectrophotometry at a wavelength of 296 nm.

Table-5: In Vitro Drug Release Studies of Formulations (F1-F8)

Time	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**
0	0	0	0	0	0	0	0	0
1	11.15	15.45	12.18	14.27	18.90	17.33	20.12	21.63
2	23.06	25.8	23.42	22.84	22.90	27.85	29.68	30.25
3	35.56	33.87	34.67	33.65	32.46	39.98	39.15	42.16
4	54.4	45.56	41.98	48.17	57.89	45.82	44.85	49.80
5	64.2	55.70	55.18	58.37	63.21	56.89	55.18	59.86
6	77.89	68.83	70.46	65.42	79.15	77.35	75.12	79.54
7	86.82	73.10	76.81	82.87	87.55	83.66	86.15	88.9
8	93.78	89.98	88.69	90.55	95.32	94.55	93.86	95.58

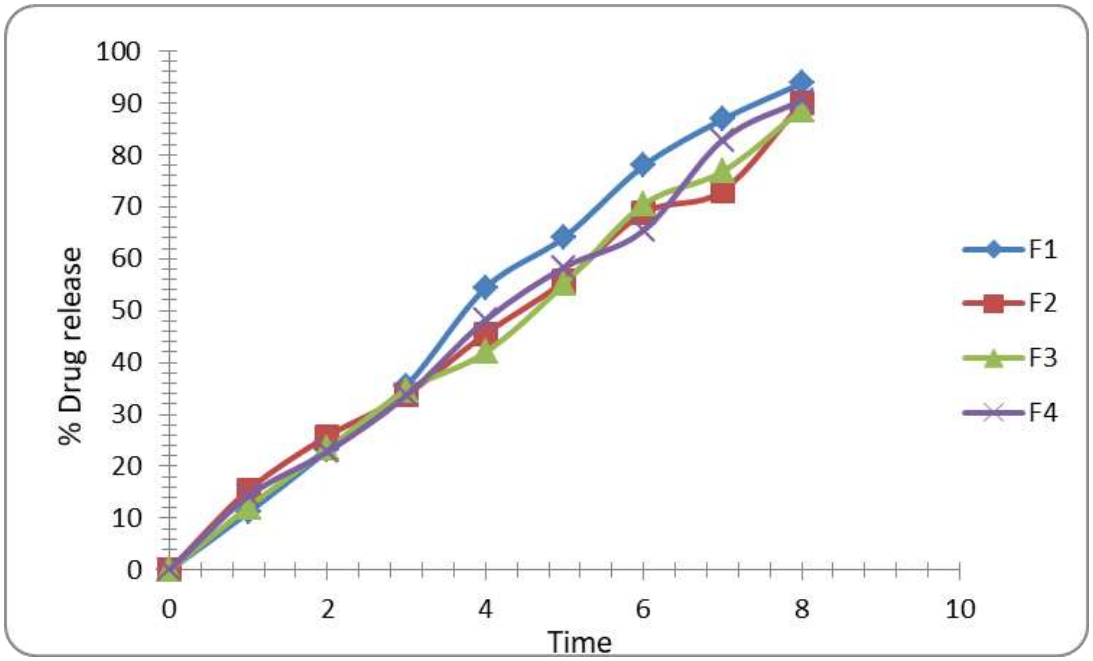

Fig-3: In Vitro Drug Release Studies of (F1-F4) Formulation

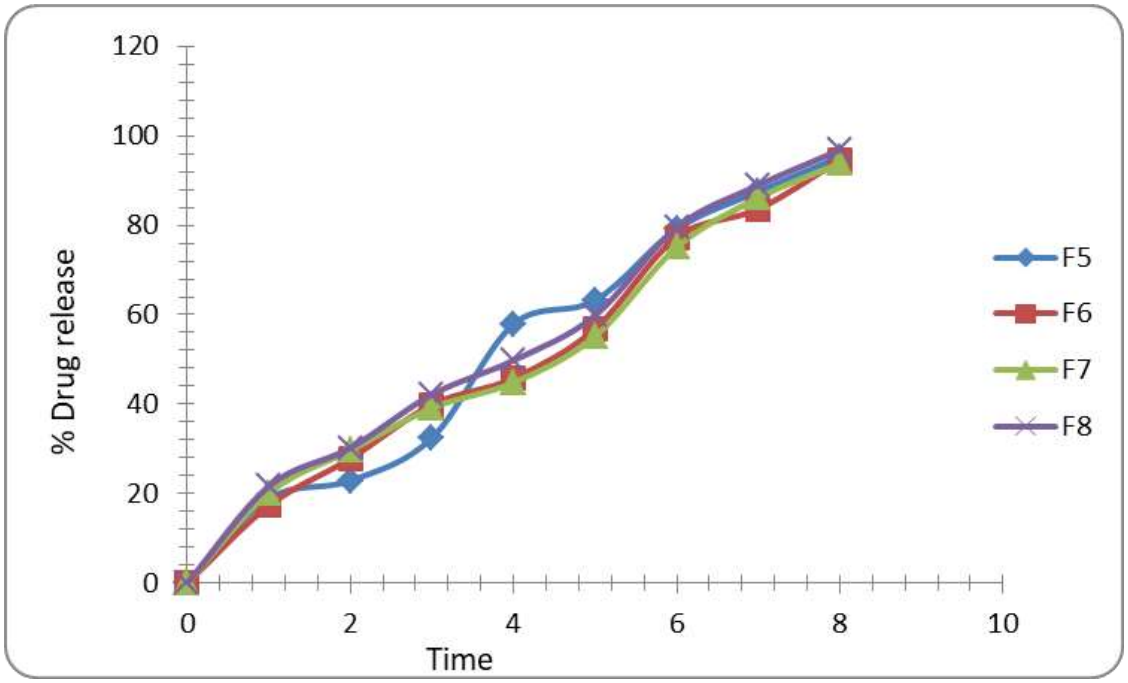

Fig-4: In Vitro Drug Release Studies of (F5-F8) Formulation

Drug Release Kinetics:

The dissolution medium utilized was 10 ml of a standard buffer with a pH of 1.2 over a specified duration. The outcomes from the in vitro release studies were analyzed using various data treatment models, which included the following:

- Cumulative percentage of drug released plotted against time (Zero Order Kinetics)
- Logarithm of cumulative percentage of drug retained plotted against time (First Order Kinetics)
- Cumulative percentage of drug released plotted against the square root of time (Higuchi's Classical Diffusion Equation)
- Logarithm of cumulative percentage release plotted against logarithm of time (Peppas Exponential Equation)

Zero Order Kinetics

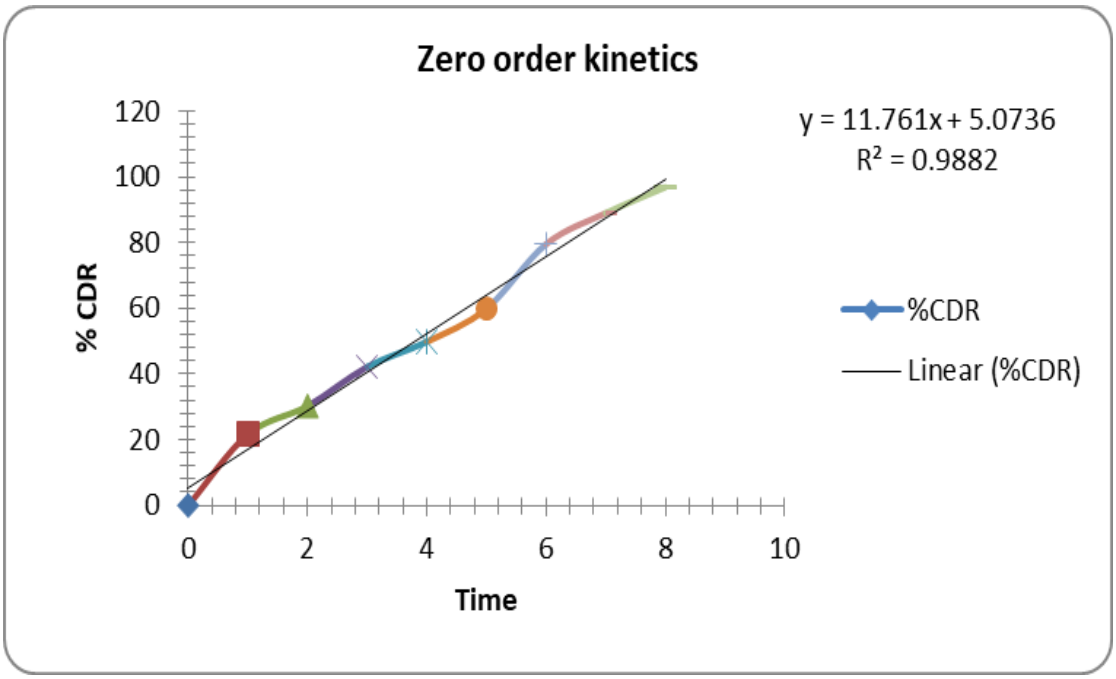

Fig-5: Zero Order Kinetics

First Order Kinetics

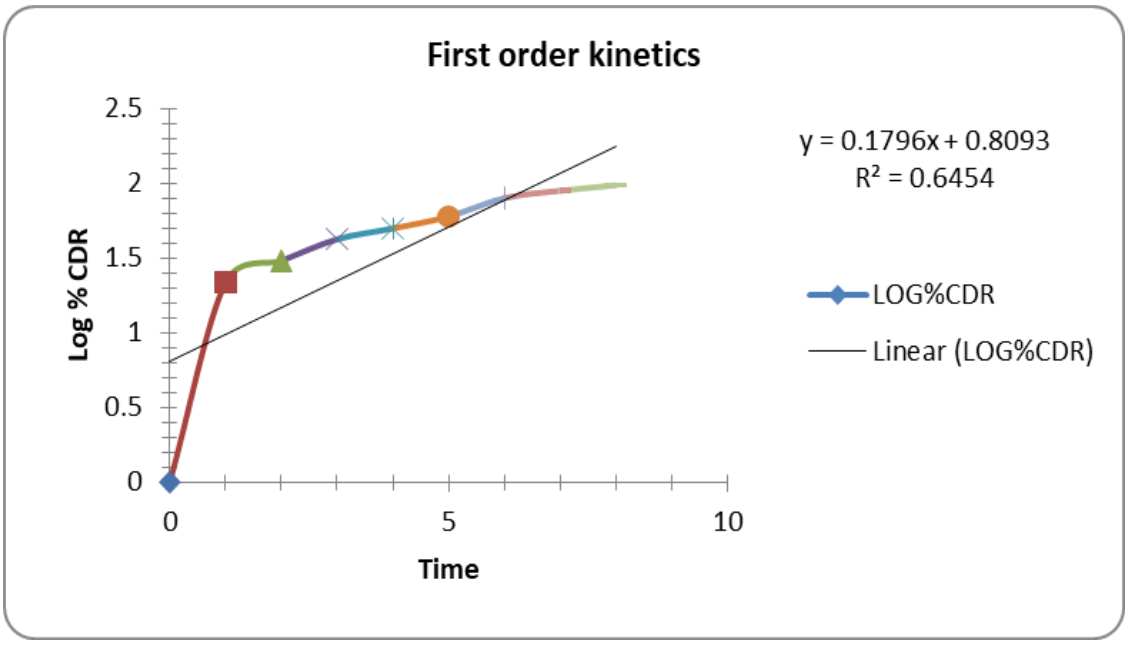

Fig-6: First Order Kinetics

Higuchi Model

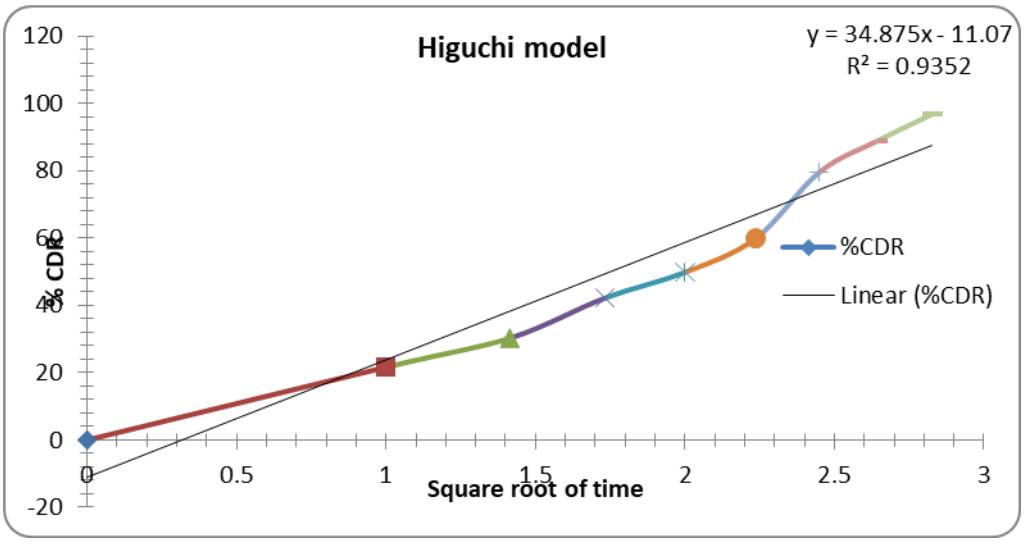

Fig-7: Higuchi Model

Korsmeyer Peppas

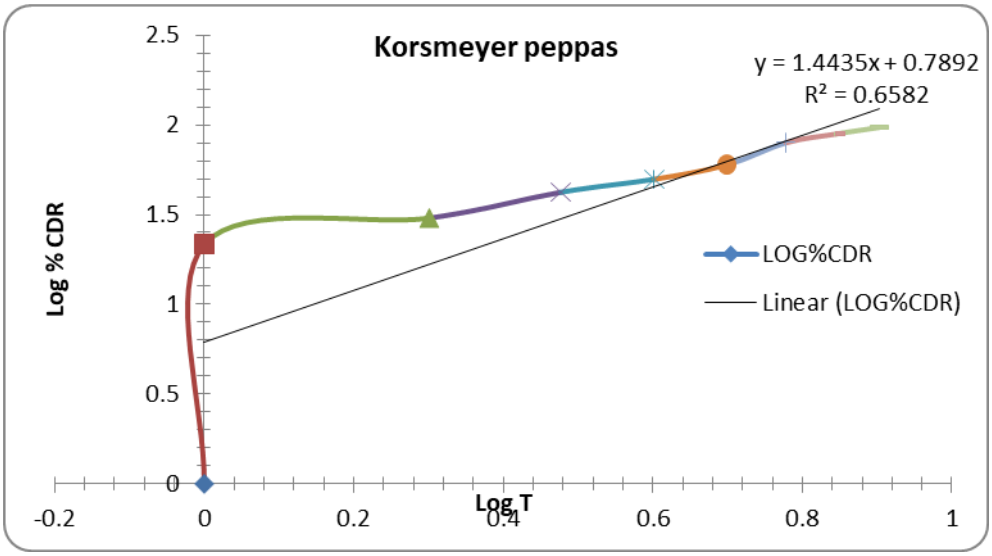

Fig-8: Korsmeyer Peppas

The in vitro release values were analyzed using various mathematical models, including zero order, first order, Higuchi matrix, and Peppas. The regression analysis indicated that the zero order release kinetics exhibited the highest values, confirming that all Vincristine nanoparticles followed this kinetic model. The data presented in the table reveal that the r² values for Higuchi's model were superior across all formulations, suggesting that the release of Tinidazole from the floating tablets adhered to a diffusion-controlled mechanism.

CONCLUSION

The primary aim of this study was to formulate floating bioadhesive tablets of Tinidazole. This research sought to enhance the gastrointestinal residence time of Tinidazole, which typically has a short gastric retention period, by developing floating tablet formulations. The tablets produced demonstrated satisfactory outcomes in various physical evaluation parameters, including dimensions, hardness, friability, weight variation, buoyancy, and content uniformity, all of which fell within acceptable limits. Among the formulations (F1-F8), formulation-8 exhibited the most favourable buoyancy and dissolution profile, establishing it as the optimal formulation.

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